08/230402

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/230,402	04/20/94	BHATTACHARJEE	A 18861128UNI

18M1/1029

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RECEIVED
OCT 30 1996

EXAMINER	
SIDBERRY, H	
ART UNIT	**PAPER NUMBER**
1802	13

DATE MAILED: 10/29/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

AMEND/APPEAL DUE 1/29/97
DRB/DIV

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/30/96

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5-18 is/are pending in the application.

Of the above, claim(s) 11-14, 18 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-3, 5-10, 15-17 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

(CF)

Form PTO 948 (Rev. 10-93) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 230402

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftspersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 6/24/97, are
A. ___ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B. X objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   ___ Not black solid lines. Fig(s)___
   ___ Color drawings are not acceptable until petition is granted.

2. PHOTOGRAPHS. 37 CFR 1.84(b)
   ___ Photographs are not acceptable until petition is granted.

3. GRAPHIC FORMS. 37 CFR 1.84 (d)
   ___ Chemical or mathematical formula not labeled as separate figure. Fig(s)___
   ___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s)___
   ___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s)___

4. TYPE OF PAPER. 37 CFR 1.84(e)
   ___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)___
   ___ Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s)___

5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes:
   21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
   21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
   21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
   21.0 cm. by 29.7 cm. (DIN size A4)
   ___ All drawing sheets not the same size. Sheet(s)___
   ___ Drawing sheet not an acceptable size. Sheet(s)___

6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Paper size	21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm. X 33.1 cm. (8 1/2 X 13 inches)	21 cm. X 29.7 cm. (8 1/2 X 11 inches)	(DIN Size A4)
T	5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5cm.
L	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	2.5 cm.
R	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.5 cm.
B	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm.

   Margins do not conform to chart above. Sheet(s)___
   ___Top (T) X Left (L). ___Right (R) ___Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   ___ All views not grouped together. Fig(s)___
   ___ Views connected by projection lines. Fig(s)___
   ___ Views contain center lines. Fig(s)___

Partial views. 37 CFR 1.84(h)(2)
   ___ Separate sheets not linked edge to edge. Fig(s)___
   ___ View and enlarged view not labeled separately. Fig(s)___
   ___ Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii) Fig(s)___

Sectional views. 37 CFR 1.84(h)(3)
   ___ Hatching not indicated for sectional portions of an object. Fig(s)___
   ___ Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s)___
   ___ Hatching not at substantial angle to surrounding axes or principal lines. Fig(s)___
   ___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)___
   ___ Hatching of juxtaposed different elements not angled in a different way. Fig(s)___

Alternate position. 37 CFR 1.84(h)(4)
   ___ A separate view required for a moved position. Fig(s)___

Modified forms. 37 CFR 1.84(h)(5)
   ___ Modified forms of construction must be shown in separate views. Fig(s)___

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   ___ View placed upon another view or within outline of another. Fig(s)___
   ___ Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)___

9. SCALE. 37 CFR 1.84(k)
   ___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)___
   ___ Indication such as "actual size" or "scale 1/2" not permitted. Fig(s)___
   ___ Elements of same view not in proportion to each other. Fig(s)___

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
   X Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s)___

11. SHADING. 37 CFR 1.84(m)
   ___ Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s)___
   ___ Solid black shading areas not permitted. Fig(s)___

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
   X Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s)___
   ___ Numbers and reference characters used in conjuction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s)___
   ___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s)___
   ___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)___
   ___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)___

13. LEAD LINES. 37 CFR 1.84(q)
   ___ Lead lines cross each other. Fig(s)___
   ___ Lead lines missing. Fig(s)___
   ___ Lead lines not as short as possible. Fig(s)___

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
   ___ Number appears in top margin. Fig(s)___
   ___ Number not larger than reference characters. Fig(s)___
   ___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)___

15. NUMBER OF VIEWS. 37 CFR 1.84(u)
   ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)___
   ___ View numbers not preceded by the abbreviation Fig. Fig(s)___
   ___ Single view contains a view number and the abbreviation Fig.
   ___ Numbers not larger than reference characters. Fig(s)___

16. CORRECTIONS. 37 CFR 1.84(w)
   ___ Corrections not durable and permanent. Fig(s)___

17. DESIGN DRAWING. 37 CFR 1.152
   ___ Surface shading shown not appropriate. Fig(s)___
   ___ Solid black shading not used for color contrast. Fig(s)___

ATTACHMENT TO PAPER NO. 12 REVIEWER [signature] DATE 7/24/97

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The examiner acknowledges the response filed 7/30/96 amending claims 1, 5, 6, 9 and 15.

Claim 4 has been cancelled.

Claims 1-3, 5-10, 15-17 are under examination.

Claims 11-14, 18 were previously withdrawn from further consideration under 37 CFR 1.1142(b) as being directed to a non-elected invention, election considered as being made without traverse in Paper No. 5.

(a) The rejection of claims 1-3, 5-10, 15-17under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's remarks.

Applicant's arguments filed 7/30/96 have been fully considered but they are not deemed to be persuasive.

(1) The objection to the specification and the rejection of now claims 1-3, 5-10, 15-15 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, failing to teach how to make and/or use the invention is maintained.

Applicant contends that the 112 1st paragraph is a "lack of utility rejection thinly disguised as a rejection on nonenablement grounds". Applicant further contends that "the Examiner cites older references that do not reflect the state of the current art".

It is noted that the Examiner acknowledges Applicants statement of "utility", as no rejection under 35 USC 101 has been set forth.

Applicant's claim a method of immunizing against gram-negative infections and against Group B meningococcal disease.

The specifications sets forth data using rabbits and the neutropenic rat demonstrating the induction of bactericidal antibody and protection against P.aeruginosa challenge, respectively.

However, it is not clear if the rabbit is an art recognized animal model of Group B meningococcal disease which correlates and is predictive of similar activity in humans.

Mandrell et al, cited, indicates that the immungenicity of meningococcal proteins in animals and their antigenicity with animal antibodies would not prove that the proteins have analogous activities in humans, as differences in the functional activities of human and animal antibodies induced by meningococcal proteins have been reported.

Moreno et al also indicate that "one should be cautious,...in attempting to extrapolate the protective value of this (Group B OMP complexed to purified B polysaccharide) from mouse models to human system(s)". (see page 532, left side)

Applicant's also claim the complex to effect protection against gram-negative bacteria or against LPS mediated pathology".

The terms infection by gram-negative and LPS mediated pathology are broadly encompassing and includes any pathological condition activated by LPS.

It is not clear if the neutropenic rat is an art accepted animals model for the generically claimed gram-negative bacteria and LPS mediated pathology.

Greenman et al, cited, teach that aside from antibiotic, surgical, and supportive care, no specific pharmacotherapy is available for gram-negative sepsis or associated organ failure.

The Examiner has further considered Applicants' submitted exhibits, however none of the exhibits appears to support Applicant's assertions that the neutropenic rat ia an animal

model for the broadly claimed vaccine and method to immunize against Group B meningococcal disease; infections by gram-negative bacteria and LPS mediated pathology.

Applicant contends that the Examiner has not demonstrated that one skilled in "this art" would find incredible the predicative value of applicants' neutropenic rat model.

Applicants claims are directed to vaccine which effects protection against group B meningococcal disease and "gram-negative" bacteria.

Applicant maintains that "vaccines have been developed against poliomyelitis, meningococcus infection, pertussis and hepatitis B infection."

The Examiner notes that existence of an "animal model" for pertussis, and the presence of "vaccines" against polio. The "vaccine" against meningococcal disease is polysaccharide protein based against serotypes A and C, not serotype group B.

However, Applicants claims are not directed to these pathogens, but to group B meningococcal disease, for which there is no vaccine and the broad vaccine "against gram-negative bacteria" which is not enabled by the specification.

Applicant has submitted various articles to traverse the issue of "animal models" raised in the 35 USC 112 1st rejection.

Exhibit 1 has been considered, however, it is unclear how this exhibit addresses the rejection of the claims under 35 USC 112, 1st paragraph. It appears to support the Examiner's position that the "LPS-mediated pathology" is a broadly generic term, as "the biologic effects are defined to include "shock, fever, leukopenia, hypoglycemia, and intravascular coagulation.".

Exhibit 3 is directed to "Future Sepsis Research" which indicates that from a "practical perspective, animal models provide insights about specific components of the septic process but cannot truly mimic the full clinical complexity and intrinsic

heterogeneity of septic patients". (see page 11 of Future of Sepsis Research)

Cross et al, was cited by the Examiner and now submitted by Applicant, does not support Applicants assertions that the "neutropenic rat is generally accepted as an animal model for determining efficacy of vaccines for immunotherapy against gram-negative bacteria and endotoxin-mediated pathology."

Cross et al does not discuss the neutropenic rat, and further states, "since animal species differ considerably in their cardiocular physiology and susceptibility to bacterial endotoxin, investigators [should] carefully considered the relative merits and limitations of each animal model before extrapolating animal data to clinical efficacy in septic patients." (see page 2741)

Romulo et al is directed to the use of monoclonal antibody directed to endotoxin or passive therapy and not the use of a complex for active immunization.

The issue regarding claim 1 which originally recited LPS, but now recites "detoxified" is resolved.

(2) The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Zollinger et al US Patent 4 707 543 is maintained.

Applicant has amended claim 1 to now recite that the lipopolysaccharide is detoxified.

However, Zollinger et al disclose complexes which may be comprised of detoxified LPS and purified OMP from N. meningitidis.

Applicant has submitted no evidence which documents a material structural and functional difference between the claimed complex and that of Zollinger et al.

(3) The rejection of claims 1-3, 5-10, 15-17 under 35 U.S.C. § 103 as being unpatentable over Zollinger et al US Patent 4

707 543 is maintained. Applicant has now amended claim 1 to recite detoxified LPS.

Applicants contend that Zollinger et al does not disclose a purified and detoxified LPS derived from E. coli and a purified OMP from N. meningitidis.

Zollinger et al disclose the use of detoxified (polysaccharide) LPS-OMP non-covalent complexes. The term "polysaccharide", according to Zollinger et al includes lipolysaccharide and capsular polysaccharide. (see column 2, lines 25-29. The detoxified lipopolysaccharide outermembrane complexes can be either noncovalently or covalently bond to form the complex. (see column 4, lines 15-22) The detoxified LPS can be derived from gram-negative bacteria, including E. coli. (see column 4, liens 25-29) The outer membrane protein being derived from N. meningitidis from serotype B. (see column 5, Example 1)

Thus, the teachings of Zollinger et al clearly suggest to one of ordinary skill in the art, the non-covalently complexing of detoxified LPS derived from gram-negative bacteria and OMP from Neisseria meningitidis serotype B.

Applicant contends that the Examiner "appears not to have appreciated the distinction between the Zollinger et al patent and the present invention."

Applicant maintains that Zollinger et al is directed primarily to the process for preparing polysaccharide-OMP complexes and to testing the bactericidal activity. "The present invention is directed to the immunoregulatory properties of a complex comprising a purified, detoxified J5 LPS and purified OMP from N. meningitidis, said properties consisting of active or passive immunization of a subject against Gram-negative bacteria and LPS-mediated pathology. Only the present J5 LPS endotoxin works in this respect".

Applicant contends that Zollinger et al proposed that an OMP-LPS vaccine would generate type-specific antibodies against meningococci that would be bactericidal for that one serotype. Applicant urges that the properties of Zollingers's complex are characterized by: the induction of type-specific antibody that can (2) enhance the killing of type-specific bacteria and utlimatlely to (3) prevent infection."

Applicant contends that the J5 subunit vaccine in the present invention is therefore entirely different is not suggested by Zollinger et al, because the invention provides antibodies that provide protection against the biologic activities of heterologous LPS and do not kill bacteria.

Applicant further urges that the "properties of the invention (the LPS-OMP complex) is "different" from that of Zollinger's. However, the claims do not contain these asserted "critical" limitations directed to the properties of the complex.

Moreover, it is noted that Zollinger et al indicate that the complexes may be used to protect against infection by the bacteria, as does Applicant.

Applicant further contends that the properties of the claimed complex are not "bactericidal", however, page 18 of the specification indicates that "bactericidal antibody response" was determined for Applicants' complex. This would appear to be contrary to Applicants remarks. It is also noted that the claims include the recitation of "actively immunizing a subject against infection by gram-negative bacteria or against lipopolysaccharide endotoxin-mediated pathology", which is not bactericidal related.

Applicant further contends, at page 11 of the remarks, that "another aspect of the present invention is evident in the demonstration that this purified and detoxified J5 LPS induces antibodies that can mediate protection independently of whole

serum, and that the IgG isotype that predominates in commercially available gammaglobulin preparations can provide protection."

It is again noted the claims do not include these asserted limitations.

It is the Examiner's position that the teachings of Zollinger et al render the claimed invention as obvious.

Zollinger et al suggest the use of detoxified LPS which may be obtained from E. coli, and non-covalently complexed with OMP from N. meningitidis serotype B as a vaccine against infection.

Although Zollinger et al does not teach the LPS to be derived from J5, the teachings of Zollinger suggest that similar results may be attained using any detoxified LPS obtained from other bacteria, as Zollinger et al indicate that "the process of this invention is generally applicable to the preparation of detoxified LPS (polysaccharide)-protein complexes derived from gram-negative bacteria, such as E. coli".

Applicant has not presented any remarks which are persuasive regarding the above maintained rejections.

The Examiner has considered the IDS submitted 1/23/96, however, no 1449 appears to have been submitted with the cited references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE

STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry of a general nature or relating o the status of this application should be directed to the Group receptionist whose telephone number is (703)-308-0196.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. F. Sidberry whose telephone number is (703) 308-0170.

Sidberry/hfs
October 23, 1996

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800